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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

MARIO PINZA, ET AL : EXAMINER: COTTON, A. M.

SERIAL NO: 10/505,178 :

FILED: AUGUST 31, 2004 : GROUP ART UNIT: 1617

FOR: DICLOFENAC-BASED COMPOSITION FOR THE TOPICAL TREATMENT OF OROPHARYNGEAL CAVITY DISORDERS:

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Now comes Mario Pinza who deposes and states:

1. That I am a named inventor of the above-identified application.

2. That I am a graduate of the University of Parma, and received my Doctoral degree in the field of Chemistry, in the year 1968.

3. That I have been employed by Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F.S.P.A, for over 14 years holding the positions of Research & Development Director and Scientific Director & General Manager, Farma Development, in the fields of Medicinal Chemistry, Synthetic Chemistry and Pharmaceutical Technology with a focus in Cognition Enhancers, Calciotropic Peptides, ß-Lactam Antibiotics, Vasodilators and Gastric Cytoprotective Agents.

4. That I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.

5. That Diclofenac tromethamine oral rinse formulations were prepared as follows:

Oral Rinse Formulations A:

Into a 200 mL vessel, complete of heater and stirrer, it was introduced:

Purified water	85 mL

The temperature was brought under stirring to 70°C and

Poloxamer 407[1]	0.500 g

was added. When the solution was completed, it was cooled to room temperature and treated in the order with:

Xylitol	10.000 g
Sodium benzoate	0.500 g
Diclofenac tromethamine[2][3]	0.104 g

When the solution was completed, always under stirring, it was introduced:

Natural mint flavor[4]	0.500 mL

and, after 10 min,:

Dye E131 (1mg/mL)[5]	0.2 mL

The solution was brought to the final weight (100 g) by addition of:

Purified water.

The pH of this formulation was 6.8.

Oral Rinse Formulations B:

Into a 200 mL vessel, complete of heater and stirrer, it was introduced:

Purified water	85 mL

The temperature was brought under stirring to 70°C and

Poloxamer 407	0.500 g

[1] All ingredients were in agreement with Eur. Ph. Unless specifically indicated.
[2] equal to 0.074 g of acidic diclofenac.
[3] Diclofenac tromethamine salt was supplied by ACRAF (Batch R3).
[4] Natural mint flavor was supplied by Selarom (Batch PL61-14).
[5] Dye E 131 was supplied by Esperis (Batch AN17008/00).

was added. When the solution was completed, it was cooled to room temperature and treated in the order with:

Xylitol	10.000 g
Sodium benzoate	0.500 g
Diclofenac tromethamine[1,2]	0.104 g

When the solution was completed, always under stirring, it was introduced:

Natural mint flavor	0.200 mL
Natural pomegranate flavor[6]	0.020 mL
Natural bubble flavor[7]	0.040 mL

and, after 10 min,:

Dye E124 (10 mg/mL)[8]	0.250 mL

The solution was brought to the final weight (100 g) by addition of:

Purified water.

The pH of this formulation was 6.8.

Oral Rinse Formulations C:

Prepared in accordance with Oral Rinse Formulation A, except the purified water was substituted with a pH 7.8 phosphate buffer. The pH 7.8 phosphate buffer was prepared as follows:

Into a 1 L volumetric flask

Anhydrous disodium hydrogen phosphate	5.803 g
Anhydrous potassium dihydrogen phosphate	3.522 g

Were dissolved in:

Purified water	900 mL

The pH value was adjusted to 7.8 by addition of:

Sodium hydroxide 1N	about	18.70 mL

[6] Natural Pomegranate flavor was supplied by Selarom (Batch 6244).
[7] Natural bubble flavor was supplied by Selarom (Batch 8060).
[8] Dye E 124 was supplied by Esperis (Batch AN18007/01).

Then the volume of the solution was adjusted to 1000 mL by addition of

Purified water.

The pH of this formulation was 7.8.

Oral Rinse Formulations D:

Prepared in accordance with Oral Rinse Formulation B, except the purified water was substituted with a pH 7.8 phosphate buffer. The pH 7.8 phosphate buffer was prepared as described above.

6. That the following stability results were obtained for the foregoing oral rinse formulations.

The starting point for the formulations was the observation that, according to the literature (Fini et al. European J. Pharm. Sci. 4, 231, 1996), the water solution of diclofenac tromethamine at a concentration of 0.104%(w/w) is clear with a pH 6.8. However, by addition of the other ingredients the resulting solution is no longer clear, the pH may fluctuate in the range of ± 0.3 units and a precipitation of small rifrangent crystals within a period of 7-15 days was observed.

In the oral rinse formulations prepared above, it was determined that oral rinse formulation A (pH = 6.8) exhibited a small amount of precipitate after 10 days at room temperature. Similarly, it was determined that oral rinse formulation B (pH = 6.8) exhibited a small amount of precipitate after 15 days at room temperature. However, when the pH of the oral rinse formulations (formulations C and D) was increased to pH 7.8 by using a phosphate buffer pH 7.8 a stable formulation is prepared without any precipitate after six months of accelerated stability (40°C; 70% R.H.).

This behaviour was entirely unexpected as regards the mouthwashes containing an amount of salt of diclofenac with tromethamine that is less than the solubility limit reported

by Fini et al. (cited above). Further, these data clearly demonstrate the criticality of the pH range of 7 to 8 as compared to the pH range of 2 to 9 which is disclosed in Cavanaugh Jr. (U.S. 5,626,838) for NSAIDs, including diclofenac. In fact, from the disclosure of Cavanaugh Jr. the skilled artisan would expect that the operating pH range of NSAIDs would be acidic (see column 5, lines 24-27 which indicates that the preferred pH is from about 4 to about 7, more preferably from about 5 to about 6). Clearly the foregoing data demonstrates that, unexpectedly, the stability advantage of the present invention is only obtained when the pH ranges from 7 to 8 rather than acidic as approximated by oral rinse formulations A and B (pH 6.8).

7. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

8. Further Declarant saith not.

Mario Pinza

Name: Mario Pinza

September 7, 2006

Date